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REVIEW

Desirable Characteristics of Hepatitis C Treatment Regimens: A Review of What We Have and What We Need

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ABSTRACT

There have been dramatic advancements in the treatment of chronic hepatitis C (HCV) infection. This is largely due to the approval of several direct-acting antiviral agents (DAAs) from a variety of medication classes with novel mechanisms of action. These therapies are a welcomed advancement given their improved efficacy and tolerability compared to pegylated interferon and ribavirin (RBV)-based regimens. These convenient, all-oral regimens treat a variety of genotypes and often offer high cure rates in a variety of HCV-infected populations. While there are several benefits associated with these therapies, there are also notable shortcomings. Shortcomings include diminished response or need for adjunctive RBV in difficult-to-treat populations (decompensated cirrhosis, active substance abuse patients, advanced kidney disease, etc.), activity against select genotypes, substantial drug–drug interaction potential, and high cost. Therefore, while current DAA-based therapies have several favorable attributes, each also has its limitations. The purpose of this review is to (1) identify the characteristics of an ideal HCV treatment regimen, (2) describe desirable features of existing regimens, (3) summarize limitations of existing regimens, and (4) introduce promising emerging therapies. This manuscript will serve as a guide for evaluating the caliber of future HCV treatment regimens.

Keywords: Effectiveness; Genotype; Hepatitis C; Pharmacotherapy; Response; Safety; Treatment

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INTRODUCTION

The emergence of direct-acting antiviral agents (DAAs) has dramatically transformed the chronic hepatitis C (HCV) treatment landscape. Compared to the historic regimen of pegylated interferon (PEG-IFN) and ribavirin (RBV), DAAs exhibit both increased tolerability and efficacy. Anticipated frequencies of sustained virologic response (SVR12), defined as an undetectable HCV RNA viral load at 12 weeks after completion of therapy, are now >90% for many DAA-containing therapies [1]. Achievement of SVR is associated with numerous health benefits including regression of fibrosis, a substantial reduction in the risk of hepatocellular carcinoma, and a 90% reduction in liver-related mortality [1]. Despite these benefits, only about 5% of the estimated 2.2–3.2 million Americans infected with chronic HCV (though nearly half are unaware of their diagnosis) receive treatment [1, 2]. While current therapies are highly efficacious and effective, many are extremely patient-specific and treatment selection is driven by viral genotype, presence of cirrhosis, use of concomitant medications, and many other considerations. They are also costly and may not be accessible to all patients. Therefore, while the approval of the DAAs is a welcomed advancement compared to therapies containing PEG-IFN and RBV, there are severable desirable traits of an "ideal" HCV therapy that have yet to be possessed by a single regimen. Emergence of this highly-desirable therapy would mean a step closer to HCV control and elimination in the United States. The purpose of this review is to (1) identify the characteristics of an ideal HCV treatment regimen, (2) describe desirable features of existing regimens, (3) summarize limitations of existing regimens, and (4) present promising emerging therapies. This review will discuss ledipasvir/sofosbuvir (LDV/SOF), paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD), simeprevir/sofosbuvir (SIM/SOF), daclatasvir/sofosbuvir (DAC/SOF), and grazoprevir/elbasvir (GZR/EBR). Given its similarity to PrOD, PrO will not be discussed [3]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

EFFICACIOUS AND EFFECTIVE

While intuitive, an ideal HCV regimen should be one that demonstrates high efficacy and effectiveness. Cure of infection is defined as achievement of sustained virologic response (SVR), or undetectable HCV RNA viral load, several weeks post-therapy completion. Historically, cure was assessed at 6 months (SVR24) after completion of up to 48 weeks of therapy. Considering that assessment at 12 weeks post-therapy completion has shown to be equally relevant [4], and that many contemporary treatment regimens are only 8–12 weeks in duration, SVR12 is the current standard [5].

Several available DAA-containing therapies have demonstrated impressive frequencies of SVR12, often greater than 90% and approaching 100%, in clinical trials [1]. SVR12 rates of currently available regimens in clinical trials are provided in Table 1. Though these findings are important for market approval, trial populations may not be fully representative of patients who will receive the treatment in practice. Therefore, an ideal treatment regimen should demonstrate not only high efficacy but also strong potential for real-world effectiveness. Favorable outcomes should be demonstrated across a spectrum of HCV-infected patients, including those who

Table 1 Characteristics of contemporary hepatitis C treatment regimens

Drug regimen	Paritaprevir/ritonavir/ombitasvir/dasabuvir	Ledipasvir/sofosbuvir	Simeprevir/sofosbuvir	Daclatasvir/sofosbuvir	Grazoprevir/elbasvir
Drug classes	NS3/4A protease inhibitor/CYP3A pharmacoenhancing agent/NS5A inhibitor/non-nucleoside NS5B palm polymerase inhibitor	NS5A protein inhibitor/NS5B polymerase inhibitor	NS3/A4 protease inhibitor/NS5B polymerase inhibitor	NS5A inhibitor/NS5B polymerase inhibitor	NS3/4A protease inhibitor/NS5A replication complex inhibitor
Efficacy					
Genotypes	1	1, 4, 5, 6	1	1, 2, 3	1, 4
Treatment-naïve non-cirrhotics	SVR = 96–97%	GT 1 SVR = 94–99% GT 4, 5, or 6 SVR = 93–96%	SVR = 93%	GT1 SVR = 96% GT3 SVR = 97%	GT1a SVR = 92% GT1b SVR = 99%
Treatment-naïve cirrhotics	GT1a SVR = 92% GT1b SVR = 100%	GT 1 SVR = 94% GT 4, 5, or 6 SVR = 93–96%	SVR = 95%	GT3 SVR = 58%	SVR = 97%
Treatment experienced non-cirrhotics	GT1a SVR = 96% GT1b SVR = 100%	GT 1 SVR = 95% GT 4, 5, or 6 SVR = 93–96%	SVR = 93%	GT3 SVR = 91–100%	SVR = 94%
Treatment experienced cirrhotics	GT1a SVR = 80–100% GT1b SVR = 86–100%	GT 1 SVR = 86–100% GT 4, 5, or 6 SVR = 93–96%	SVR = 86% (12 weeks) SVR = 100% (24 weeks)	GT3 SVR = 86%	SVR = 95%
HIV coinfection	GT1a SVR = 91% GT1b SVR = 100%	GT 1 or 4 SVR = 96%	SVR = 77% from observational effectiveness study	GT 1 no cirrhosis SVR = 98% GT 1 cirrhosis SVR = 91% GT3 SVR = 100%	SVR = 96%
Convenience					
Dosing	Two tablets daily (75/50/12.5 mg) and 250 mg tablet twice daily	One tablet daily (90 mg/400 mg)	150 mg daily/400 mg daily	60 mg daily/400 mg daily With strong CYP3A inhibitors—30 mg daily of daclatasvir With moderate CYP3A inducers—90 mg daily of daclatasvir	100 mg/50 mg daily
Food requirement	With food	With or without food	With food	With or without food	With or without food
Need for ribavirin	Use ribavirin except in non-cirrhotic GT1B patients	Can be considered in treatment experienced GT 1 patients with cirrhosis who are eligible or patients with decompensated cirrhosis	No	Can be considered in presence of cirrhosis	Use ribavirin if baseline NS5A resistance-associated variants

Table 1 continued

Drug regimen	Paritaprevir/ritonavir/ombitasvir/dasabuvir	Ledipasvir/sofosbuvir	Simeprevir/sofosbuvir	Daclatasvir/sofosbuvir	Grazoprevir/elbasvir
Duration	12 weeks, except for GT1a with cirrhosis is 24 weeks	Treatment naïve without cirrhosis and baseline HCV RNA <6 million GT1 = 8 weeks Treatment naive with or without cirrhosis GT 1, 4, 5 or 6 = 12 weeks Treatment experienced without cirrhosis GT 1, 4, 5 or 6 = 12 weeks Treatment experienced with compensated cirrhosis GT 1 = 24 weeks or 12 weeks with ribavirin GT 4, 5, 6 = 12 weeks Decompensated cirrhosis GT 1 or 4 = 12 weeks	Treatment naive or experienced without cirrhosis 12 weeks Treatment naive or experienced with cirrhosis 24 weeks	12 weeks Cirrhosis: GT1: 24 weeks GT2: 16–24 weeks GT3: 24 weeks	12 weeks 16 weeks in the presence of NS5A resistance-associated variants
Single tablet regimen	No (first 3 drugs are a combination tablet in addition to dasabuvir tablets)	Yes	No	No	Yes
Safety					
Adverse events	Common-fatigue, nausea, pruritus, skin reactions, insomnia, asthenia Hepatic decompensation and heart failure in patients with cirrhosis Increased risk of ALT elevations	Common-fatigue, headache, nausea, diarrhea, insomnia Serious symptomatic bradycardia when coadministered amiodarone If administered with RBV-diarrhea, N/V, loss of appetite, asthenia, neutropenia, dizziness, hemolytic anemia (serious)	Common-fatigue, headache, nausea Serious symptomatic bradycardia when the combo is administered with amiodarone Hepatic decompensation and heart failure have also been seen in patients with advanced or decompensated cirrhosis Photosensitivity and rash	Common-fatigue, nausea, headache, diarrhea Serious symptomatic bradycardia when the combo is administered with amiodarone	Common-fatigue, headache, nausea With ribavirin—anemia and headache Serious—ALT elevations

Table 1 continued

Drug regimen	Paritaprevir/ritonavir/ombitasvir/dasabuvir	Ledipasvir/sofosbuvir	Simeprevir/sofosbuvir	Daclatasvir/sofosbuvir	Grazoprevir/elbasvir
Special notes	Numerous drug interactions due to ritonavir component	No dosage recommendation can be given for patients with severe renal impairment (CrCl <30 mL/min) or with ESRD due to high exposures of sofosbuvir metabolite	Safety and efficacy has not been established with sofosbuvir in patients with CrCl <30 ml/min or patients on hemodialysis	Safety and efficacy has not been established with sofosbuvir in patients with CrCl <30 ml/min or patients on hemodialysis Dose of daclatasvir may need to be altered when concomitantly used with other CYP3A inhibitors or inducers	Can be used in chronic kidney disease (CKD) stages 4 and 5, including patients on hemodialysis

are relatively healthy and treatment-naïve ("uncomplicated") as well as those considered more difficult-to-treat or "complicated" based on individual history and comorbidities. These patients may be treatment-experienced, with high baseline viral loads and genetic variants (e.g., Q80K in the context of simeprevir-containing regimens), have various coinfections such as human immunodeficiency virus (HIV) or hepatitis B, and/or have advanced liver disease (e.g., decompensated cirrhosis). Historically, these patients have diminished treatment responses and higher risks of HCV-associated complications relative to treatment-naïve, HCV mono-infected patients with no evidence of liver damage or cirrhosis [1].

Consistent with expected outcomes from the ideal treatment regimen, several available therapies have demonstrated substantial efficacy in difficult-to-treat patients, though adjunctive RBV is often required. Cure rates with DAA-based therapies, which often exceed 90%, are staggering compared to those associated with PEG-IFN and RBV treatment, which were approximately 17% for cirrhotic patients, for example [6].

However, probability of cure remains highly patient- and regimen-specific (e.g., presence of the Q80K mutation in GT1a-infected, treatment-experienced, cirrhotic patients is associated with failure to SIM/SOF) [7, 8]. Several populations face limited treatment options, including those with less common GTs, renal disease, pregnant women, post-transplant recipients, and previous DAA-based therapy failures [1]. Additionally, treatment would still prove successful in populations unlikely to be included in trials or large studies, including those with a recent history of substance use, advanced age, and psychiatric illness. Despite numerous

patient-specific challenges that complicate effectiveness of available HCV therapies, the ideal treatment regimen would result in high probability of SVR12 consistently across all HCV-infected populations without need for adjunctive medications such as RBV.

SAFE

Non-Toxic

HCV treatment-associated toxicity was a considerable patient care hurdle prior to 2013 when PEG-IFN and RBV continued to be included in the mainstay of treatment. Given its association with several adverse effects and laboratory abnormalities, PEG-IFN plus RBV required close safety monitoring. In some cases, supplementary medications were required to treat or manage HCV treatment-associated adverse effects (e.g., epoetin alfa to treat drug-induced anemia). In a contemporary setting, an ideal HCV treatment should be tolerable and unlikely to cause laboratory abnormalities. The latter is important as frequent laboratory testing during and potentially post-treatment are inconvenient and costly. Lack of both tolerability and overall treatment safety may lead to possible patient harm, premature discontinuation of therapy, and/or poor adherence leading to unsuccessful cure.

Most contemporary HCV regimens demonstrated high tolerability in clinical trials, with infrequent therapy discontinuations from serious adverse events. For DAC/SOF and LDV/SOF, the most commonly reported adverse events were minor, including fatigue and headache [9, 10]. For SIM/SOF, a unique adverse effect is a variety of dermatologic manifestations including rash and pruritus. This typically occurs within 4 weeks of therapy initiation and may be due to certain drug chemical properties (e.g., SIM has a sulfa-like moiety) and/or photosensitivity potential [7]. PrOD, though generally well-tolerated in clinical studies, may cause serious hepatic injury. Patients with advanced liver disease appear to be particularly susceptible, as described in a recently issued FDA warning [3, 11]. Additionally, PrOD is often co-administered with RBV, which can cause hemolytic anemia. Considering the toxicity potential of many currently available HCV therapies, an ideal treatment regimen would have a favorable toxicity profile with minimal risk of serious adverse events.

Devoid of Drug–Drug Interactions

While adverse effects of each regimen should be considered, it is also important to assess the safety of anti-HCV agents when given concomitantly with other medications. Drug–drug interactions (DDIs) are of substantial concern in the HCV-infected population, given that treatment regimens consist of multiple treatment medications for patients that frequently have medically managed comorbidities [12]. Many interactions involve the cytochrome (CYP) P450 isoenzyme system, including CYP3A4, which metabolizes DAAs and several other classes of medications [7]. Among the HCV regimens, SIM is an inhibitor of intestinal CYP3A4 and the ritonavir component of PrOD is involved in the hepatic inhibition of CYP3A4 as well as several other CYP isoenzymes [7, 11]. GZR is a weak inhibitor of CYP3A4 and may be implicated in fewer interactions [13]. LDV and EBR are inhibitors of p-glycoprotein (PGP) and breast cancer receptor protein (BCRP) [9, 13]. DAC is an inhibitor of PGP and organic anion transporter protein (OATP) 1B1 [10].

DDIs involving each of the HCV regimens and common classes of medications are displayed in Table 2. HMG-CoA reductase inhibitors (statins) are a popular medication class subject to numerous DDIs with HCV therapies, and management is agent-specific. One of the most serious DDIs identified with DAAs is coadministration of SOF and amiodarone, which can result in severe bradyarrhythmias. Coadministration is contra-indicated and patients using amiodarone should avoid SOF-containing therapy [9, 14–16].

Within the HIV/HCV co-infected population, DDIs with antiretrovirals are of particular concern. Most protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are problematic for GZR/EBR, SIM/SOF and PrOD [7, 11, 13]. For LDV/SOF, increased exposure (AUC) to tenofovir disoproxil fumarate (TDF) is observed in HIV/HCV co-infected patients using efavirenz or protease-inhibitor containing regimens [9]. However, the degree of enhanced exposure observed with efavirenz and TDF coadministration with LDV/SOF is still within the range of tenofovir AUC values in which safety data exist. For regimens containing PIs and TDF that are coadministered with LDV/SOF, the upper bound of the confidence interval slightly exceeds the range of tenofovir AUC values in which safety data exist. The future impact of the TDF interaction is unknown as use of tenofovir alafenamide (TAF) becomes more widespread. Dolutegravir and raltegravir appear to be the safest options for coadministration with HCV therapy. When considering DDI management, a key limitation of many available HCV therapies is the coformulation of multiple antivirals in a single product. Currently, dose personalization/adjustment of individual agents associated with an interaction or toxicity within a co-formulated product is unfeasible. As currently available HCV therapies pose notable risks for potentially serious DDIs, elimination of this potential would be an important attribute of an ideal treatment regimen.

CONVENIENT

An ideal HCV treatment regimen would have convenient all oral administration. Reducing pill burden and decreasing regimen complexity are associated with improved clinical outcomes in other therapeutic domains and may extend to HCV [17–19]. In the HIV-infected population, use of single tablet regimens (STRs) is associated with improved medication adherence to antiretroviral therapy and decreased hospitalizations [20–22]. Similar conclusions cannot be made in the context of HCV infection, as studies have not yet been performed comparing medication adherence to single- versus multiple-tablet regimens and the effect of number of tablets per day on achieving SVR. In HCV, a single oral tablet formulation dosed infrequently (e.g., daily) for a short treatment duration would appear most desirable, largely due to convenience. However, the convenience of a single-tablet regimen needs to be tempered with a discussion of the relationship between non-adherence and resistance. It is unclear if non-adherence to a single-tablet regimen results in a higher potential for development of drug resistance than multiple-tablet regimens dosed multiple times per day. A thorough understanding of the pharmacokinetic/pharmacodynamics indices associated with the development of resistance will be imperative and predominantly applicable to missing doses of medications with short half-lives. This is an important area

Table 2 Summary of drug–drug interactions with hepatitis C treatment regimens

	Paritaprevir/ritonavir/ ombitasvir/dasabuvir	Ledipasvir/sofosbuvir	Simeprevir/sofosbuvir	Daclatasvir/sofosbuvir	Grazoprevir/elbasvir
Avoid combination	Alpha 1-antagonist (alfluzosin); Anticonvulsants; antifungals (voriconazole); Antihyperlipidemic (gemfibrozil); Antimycobacterial (rifampin); beta adrenoceptor agonist (salmeterol); corticosteroids (fluticasone); ergot derivatives; ethinyl estradiol containing products; herbal products (St. John's Wort); HMG-CoA reductase inhibitors (lovastatin and simvastatin); neuroleptic (pimozide); phosphodiesterase-5 inhibitor (sildenafil when used for pulmonary arterial hypertension); sedative/ hypnotics (midazolam, triazolam); integrase inhibitors (elvitegravir, dolutegravir); NNRTIs (efavirenz, etravirine, nevirapine, rilpivirine, zidovudine, didanosine); protease inhibitors (darunavir/ r, fosamprenavir, ritonavir, lopinavir/r, tipranavir, saquinavir)	Antiarrythmics (amiodarone); anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin); antimycobacterials (rifampin, rifabutin, rifapentine); herbal products (St. John's Wort); simeprevir; elvitegravir when coadministered with tenofovir disoproxil fumarate, emtricitabine and cobicistat; tipranavir/r	Antiarrythmics (amiodarone); antibiotics (clarithromycin, erythromycin, telithromycin); anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin); antifungals (fluconazole, itraconazole, ketoconazole, osaconazole, voriconazole); Antimycobacterials (rifampin, rifabutin, rifapentine); corticosteroids (dexamethasone); herbal products (milk thistle, St. John's Wort); GI motility agents (cisapride); elvitegravir; NNRTIs (efavirenz, etravirine, nevirapine); protease inhibitors (atazanavir, fosamprenavir, indinavir, lopinavir/r, ritonavir, saquinavir, tipranavir, darunavir/r)	Antiarrythmics (amiodarone); anticoagulant (dabigatran—depends on renal group); anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin); antimycobacterials (rifampin, rifabutin, rifapentine); herbal products (St. John's Wort); Tipranavir/r	Anticonvulsants (phenytoin, carbamazepine); antimycobacterials (rifampin); herbal products (St. John's Wort); NNRTIs (efavirenz, etravirine); protease inhibitors (atazanavir, lopinavir, saquinavir, tipranavir, darunavir); immunosuppressants (cyclosporine); antibiotics (nafcillin); antifungals (ketoconazole); endothelian antagonists (bosentan); integrase inhibitors (elvitegravir coformulated with either tenofovir disoproxil fumarate or alafenamide with emtricitabine and cobicistat); wakefulness agents (modafinil)
Requires enhanced monitoring	Antiarrythmics (amiodarone, bepredil, disopyramide, flecainide, lidocaine, mexilitine, propafenone, quinidine); diuretic (furosemide); narcotic analgesics (naloxone); proton pump inhibitors; sedative/ hypnotic (alprazolam)	Digoxin; NNRTIs (etravirine, nevirapine, efavirenz)	CCBs; Digoxin	Antiarrythmics (digoxin); HMG-CoA reductase inhibitors	HMG-CoA reductase inhibitors (fluvastatin, lovastatin, simvastatin); Immunosuppressants (tacrolimus)

Table 2 continued

	Paritaprevir/ritonavir/ombitasvir/dasabuvir	Ledipasvir/sofosbuvir	Simeprevir/sofosbuvir	Daclatasvir/sofosbuvir	Grazoprevir/elbasvir
Requires modification of dose or administration of one or both agents	Antifungal (fluconazole); calcium channel blocker (amlodipine); HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin, and pravastatin); immunosuppressants (cyclosporine, tacrolimus); Phosphodiesterase-5 inhibitor (when used for ED)	H2-receptor antagonists; proton-pump inhibitors; antacids (separate by 4 h); HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin)	HMG-CoA reductase inhibitors; sedative/hypnotics (midazolam, triazolam)	Antibiotics (clarithromycin, erythromycin, nafcillin); antifungals (itraconazole, ketoconazole; posaconazole; voriconazole); antimycobacterials (rifapentine); endothelian antagonists (bosentan); INSTI (elvitegravir with tenofovir disoproxil fumarate, emtricitabine and cobicistat); NNRTIs (efavirenz, etravirine, nevirapine); protease inhibitors (atazanavir boosted with either cobicistat or ritonavir, indinavir, nelfinavir and saquinavir); wakefulness agents (modafinil)	HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin)

for evaluation in future studies as use of these regimens becomes more widespread. Regardless, strategies to improve adherence should still be maximized, which include patient education, frequent monitoring or contact from clinicians, and patient devices to enhance adherence (alarm clocks, pill boxes, text reminders, etc.).

The convenience of HCV treatment has improved dramatically. Historically, treatment regimens consisted of daily or thrice weekly injections used in combination with high pill-burden oral medications that were dosed multiple times a day for up to 48 weeks [1]. Today, several HCV treatments possess select attributes of an ideal regimen. LDV/SOF and GZR/EBR offer the convenience of single, fixed-dose combination tablet regimens, substantially decreasing treatment pill burden [9, 13]. Dosing frequency has also improved given that the majority of HCV treatment regimens for GT1 infection are dosed once daily [7, 9, 10, 13]. The exception to this is the dasabuvir component of the PrOD regimen, which is dosed twice daily [11]. While the remaining regimens may be administered once daily, some may require concomitant use of twice daily RBV, particularly in patients with cirrhosis and who have previously failed therapy [7, 9–11, 13]. Unlike the traditional interferon-based 48-week treatment course, most DAA HCV regimens are 12 weeks in duration. Post hoc findings from ION-3 suggest 8 weeks of LDV/SOF may be appropriate for treatment-naïve, non-cirrhotic, GT1-infected patients with baseline HCV RNA <6 million IU/mL [9, 23]. Similar suggestions have been made for SIM/SOF in GT1-infected patients with HCV RNA threshold of 4 million IU/mL [8, 24]. Though not prospectively validated or endorsed by guidelines, these findings suggest the

possibility of shorter treatment courses without compromised efficacy for select populations. GZR/EBR plus RBV for 8 weeks may offer another abbreviated treatment option, though SVR rates were <90% [25]. Ideally, future regimens will offer a short course of conveniently administered therapy for all HCV patient populations.

ACCESSIBLE AND AFFORDABLE

An ideal HCV regimen will be one that is affordable and relatively easy to obtain for patients from all socioeconomic backgrounds. Many of these therapies are offered through patient assistance programs to increase accessibility and affordability for qualifying individuals. However, many patients with HCV infection face numerous barriers hampering access to optimal therapy [26]. In the US, barriers include high treatment costs, lack of third party payer coverage or coverage contingencies, requirement for prior authorization approval, and therapy restriction to only patients with severe infection. These limitations and restrictions greatly complicate patient access to appropriate HCV treatment. This is particularly concerning given the evidence that delays in therapy are associated with an increased risk of adverse HCV-associated outcomes [1].

The most widely discussed barrier is the high treatment cost, which may not be affordable out-of-pocket for the vast number of HCV-infected patients that are uninsured or underinsured [13]. While the true cost of these medications to third party payers is largely unknown due to proprietary contract pricing, average wholesale pricing of many 12-week courses of DAA treatments are in excess of US$90,000 for the medication alone (i.e. monitoring and clinic visit costs are not included in this price) [10]. Currently, the least expensive regimen is the newly-approved GZR/EBR, costing approximately US$55,000 [11]. For those with prescription insurance, high copayments or deductibles may still exist. Additionally, while manufacturer-based patient assistance programs exist for the DAAs, some are associated with income restrictions or manufacturer specific guidelines for treatment [27].

If a patient does have prescription insurance, various restrictions to DAA coverage may apply. One restriction is prior authorization (PA), whereby clinicians must provide written justification to a third party payer as to why the medication is necessary for the patient. Additional patient requirements may include urine toxicology panels, urine pregnancy tests, or a consent form by which the patient pledges adherence to medication therapy and follow-up appointments. This added layer of approvals imposed by some third-party payers requires dedicated resources that may not be taken into account by many cost-effectiveness models [28]. Restrictions may also apply for severity of infection, which is commonly characterized by the METAVIR score that assesses liver necroinflammation and fibrosis. One study indicated that among the 42 states with known Medicaid restriction criteria for SOF, 74% limit treatment to patients with the highest METAVIR scores of F3 or F4 [29]. There is limited evidence to support some of the aforementioned requirements [1]. However, with more widespread use of DAA-containing regimens, there may be more evidence in the future to support or refute HCV "stewardship," such as rationing new agents for difficult patients and inexpensive agents for less complex patients. Notably, many of the logistical issues described above are unique to the US and may not be germane to other

geographic locales, or in the future with movement towards universal healthcare coverage. As more HCV-infected patients obtain access to treatment, infection rates by transmission may decline and subsequently decrease the overall societal and financial burden of HCV. An ideal regimen would be affordable and accessible for all patients seeking treatment.

HIGH BARRIER TO RESISTANCE

High efficacy demonstrated by several HCV regimens means treatment success for many patients. However, in the event of relapse or treatment failure, an ideal therapy would exhibit a high barrier to resistance with little potential for cross-resistance with other agents. Some regimens are affected by baseline NS5A mutations. Among GT1A-infected patients receiving 12 weeks of GZR/EBR, SVR was lower among patients with at least one baseline NS5A resistance-associated polymorphism at amino acid positions 28, 30, 31 or 93 [3, 9]. Thus, patients with GT1A infection initiating GZR/EBR need to undergo NS5A testing. The presence of any of these four polymorphisms extends therapy from 12 to 16 weeks and requires the addition of ribavirin [3, 9]. As the use of NS5A inhibitors becomes more ubiquitous and the issues of cross-resistance and persistence of NS5A and NS3 mutations are better understood, the impact of this test may become applicable to other treatment regimens. Findings may steer certain patient populations from using these therapies. Cross-resistance exists for some available agents including the protease inhibitors, SIM and paritaprevir [7, 11]. SOF is advantageous in that it exhibits a high barrier to resistance and, when used in combination with other DAA agents, may still be used successfully to overcome the presence of baseline antiviral resistance-associated variants (RAV) [9, 16]. LDV/SOF may offer a promising treatment option for patients who have failed a RBV-containing regimen or SIM/SOF (though addition of RBV to LDV/SOF is recommended for the latter); however, data are limited [9]. PEG-IFN, though no longer a component of most preferred regimens, maintains activity in the setting of RAVs and therefore remains a viable adjunctive option for many treatment-experienced patients [1].

FUTURE DIRECTIONS

Several promising HCV treatment regimens with "ideal" traits lie just over the horizon. A novel NS5A inhibitor, velpatasvir (GS-5816), in combination with SOF for 12 weeks, has produced SVR12 rates >90% in patients with GT1 through 6 in various stages of clinical study [26, 30]. Cure was still achieved in most patients exhibiting baseline genetic viral variants for NS5A. While larger studies including more difficult-to-treat populations are needed, such as those with cirrhosis and history of treatment failure, preliminary results are encouraging [27]. A pangenotypic option, if possessing other traits of an ideal regimen, could increase accessibility of treatment for all HCV-infected patients, particularly those with currently limited treatment options based on specific genotypes. In addition to regimens offering broad-spectrum genotypic activity, shorter treatment durations are also being pursued. Several 4- and 6-week combination therapy regimens (2–3 agents) are being explored in phase II studies that will hopefully add additional highly efficacious, multigenotypic therapies to the growing HCV treatment armamentarium [30]. Though further beyond

the horizon, emergence of generic treatment options will likely alter the treatment landscape once again. A series of questions will arise pertaining to cost-effectiveness of branded single-tablet regimens versus less expensive multiple-tablet regimens and the impact on regimen adherence and ultimate treatment success.

CONCLUSIONS

As the treatment landscape for chronic HCV infection continues to rapidly evolve, the characteristics associated with an ideal regimen remain constant. An ideal regimen is one that is efficacious in a variety of populations, convenient, safe, accessible/affordable, and has a high barrier to resistance. Although significant progress has been made, no commercially available regimen fully achieves each of these desirable characteristics. It is imperative for continued research and development to achieve these goals to produce dramatic reductions in HCV infection burden globally.

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